UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Date: December 11, 2000

MEMORANDUM

SUBJECT: **ENDOSULFAN:** Evaluation of Registrant Submission *Endosulfan: Evaluation of Possible Endocrine Effects in Mammalian Species.*

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On June 16, 2000 the Health Effects Division (HED) in the Office of Pesticide Programs (OPP) issued a Risk Assessment for the Endosulfan Reregistration Eligibility Decision (RED) Document. As part of the hazard characterization required for a risk assessment, the toxicological database for endosulfan was reviewed and evaluated. In the process of this evaluation, endosulfan was identified as a potential endocrine disruptor.

The registrant, AgrEvo, has submitted a literature review in response to the Agency's characterization of the endosulfan database as providing "suggestive evidence that endosulfan may be an endocrine disruptor." After reviewing several published articles, the registrant concludes that "endosulfan does not meet the criteria of an endocrine disruptor." The registrant states that *in vitro* studies show that endosulfan has a low binding potency to the human estrogen receptors and that "no effects were found on endocrine, reproductive or sexually regulated systems *in vivo* at doses causing clear toxicity."

The Agency identifies an environmental endocrine disruptor as an exogenous agent that interferes with the synthesis, secretion, transport, binding action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior.[1] Based on these criteria, the Agency disagrees with the conclusion by the registrant that endosulfan does not meet the definition of an endocrine disruptor. Binding to the estrogen receptor is only one potential mode of action for endocrine disruptors, namely direct interaction with a receptor in the target cells. Substances that act as endocrine disruptors may perturb the endocrine system in a variety of ways including but not limited to interfering with the synthesis, secretion, or transport of hormones in the organism. Consequently, the absence of high binding affinity to the estrogen receptor should not be interpreted as lack of endocrine disruption potential. The Agency notes that other organochlorines (i.e. DDT, DDE, dieldrin, and methoxychlor) have been demonstrated to interact with the endocrine system in spite of differing binding affinities to the estrogen receptor . Finally, the registrant states that no effects were reported after administration of endosulfan on the endocrine, reproductive or sexually regulated systems at doses causing clear toxicity. However, it is noteworthy that testicular atrophy was reported during a Chronic Oral Toxicity Study in Rats (MRID 00004256) submitted to the Agency. Additionally, increased pituitary and uterine weights were also observed during a Multi-Generation Reproduction Study (MRID 00148264). Furthermore, an increase in the incidence of parathyroid hyperplasia was also reported during the Chronic Oral Toxicity study in Rats. The Agency emphasizes the fact that the endocrine system integrates a variety of CNS-pituitary-target organ pathways that not only affect reproductive or sexually regulated parameters but also regulates a wide array of bodily functions and homeostasis.[2] Though this is not the case for endosulfan, it is important to note that a lack of overt toxicity to the reproductive system should not be interpreted as conclusive evidence of a lack of endocrine disruption. Given the effects noted in the Chronic Oral Toxicity Study in Rats and the Multi-Generation Reproduction Study submitted to the Agency, the potential of endosulfan to act as an endocrine disruptor can not be discounted. The Agency has requested that a Developmental Neurotoxicity Study be conducted; the Agency believes that this study will provide additional data that may help elucidate this matter.

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[1] Crisp, T.M. *et al. Environmental Endocrine Disruption: An Effects Assessment and Analysis.* **Environmental Health Perpectives 106 pp. 11-56.**

[2] R.L. Cooper and R.J. Kavlock. *Endocrine Disruptors and Reproductive Development: a Weight-of Evidence Overview.* **J. Endocrinology 152 pp. 159.-166**